Patients with chronic periodontitis are more likely to develop upper urinary tract stone: a nation-wide population-based eight-year follow up study (#24824)

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Patients with chronic periodontitis are more likely to develop upper urinary tract stone: a nation-wide population-based eight-year follow up study

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Background This purpose of this study was to investigate associations between chronic periodontitis (CP) and upper urinary tract stone (UUTS) in Taiwan by using population-based data set.

Methods A total of 16,292 CP patients and randomly selected 48,876 controls without chronic periodontitis were selected from the National research database and studied retrospectively. Subjects selected have not been diagnosed of UUTS previously. These subjects were prospectively followed for at least eight years. Cox regression model were used to explore the connection between risk factors and the development of UUTS.

Results The CP patients have greater chance of developing UUTS comparing to controls (1761/16292, 10.8% vs 4775/48876, 9.8%, p-values < 0.001). Conditioned logistic regression suggested CP increase the risk of UUTS development (HR 1.14, 95% CI, 1.08–1.20, p < 0.001). After adjusting for age, gender, hypertension and diabetes, result showed that CP still increase the risk of developing UUTS (HR 1.14, 95% CI = 1.08–1.20, p < 0.001).

Conclusion By using population based database with a minimum eight year follow-up of CP in Taiwan, we discovered CP increase the risk of developing UUTS.

Original article

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Conflicts of interest:

The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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Abstract

Background

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Keywords: Chronic periodontitis, urolithiasis, upper urinary tract stone

Introduction

Urolithiasis is common urological disease with prevalence ranging from 5% to 20%, and varies with gender, age, race and geographical region (Scales et al., 2012; Hall et al., 2009; Stamatelou et al., 2003). The incidence has increased in the US in the last three decades and for Taiwanese population, an increase of 8.9% in men between 1998 to 2010 (Huang et al., 2013). Recurrence rate was 6-10% within one year and up to 35-50% during five year follow up (Huang et al., 2013; Pearle et al., 2005; Penniston et al., 2011). The high prevalence and recurrence rate represent significant cost burden to the healthcare system, especially for the population in their 40s to 50s, where the annual expenditure is estimated to exceed $5 billion, including direct (treatment) and indirect (work productivity) cost (Penniston et al., 2011; Saigal et al., 2005).

Chronic periodontitis (CP) is ~~another~~ prevalent inflammatory disease of tooth-supporting tissue, caused by oral bacterial infection and resulting in dysregulation of host immuno-inflammatory response. In the United States, adult aged 30 years or older have an estimated prevalence of 45% and CP is positively correlated with increased age and male gender (Eke et al., 2012). In CP, action of matrix degrading enzyme and lipopolysaccharide from oral bacteria trigger aggregation of interleukin and tumor necrosis factor, which amplify the inflammatory response and reduce the damage repair ability of fibroblast, leading to osteoclastogenesis activation and subsequent alveolar bone damage (Armitage et al., 2003; Schenkein et al., 2006). Inflammation from CP could also lead to exposure of extracellular damage-associated molecular patterns (DAMPs), that can initiate and perpetuate a noninfectious inflammatory process (Shields et al., 2011). Uric acid may possible be presented during DAMPs metabolism and ~~also~~ a risk factor for stone formation (Jounai et al., 2012). In addition, during the progression and development of CP, bone metabolism and bone remodeling are altered and the marker of bone metabolism could be used as reflection of its progression (Yoshihara et al., 2009). In patients with severe periodontitis, the levels of parathyroid hormone (PTH) were higher and levels of ~~25(OH)D~~ were lower, indicating that compare to normal subject, CP patient may have more serious bone resorption and demineralization (Schulze-Späte et al., 2015).

Due to elevated PTH and uric acid metabolite in CP patients and because they are risk factors for urolithiasis, we hypothesize that CP can potentially induce urolithiasis. This is this first reported study exploring the relationship between CP and urolithiasis. We analyzed the connection between initial chronic periodontitis and subsequent risk of urolithiasis during the eight-year follow up period with nationwide population database.

Materials and Methods

Data Source

The National Health Insurance (NHI) launced, by the department of Health in Taiwan has prospectively collected original data for reimbursement, and since by the end of 1996, over 95% of the Taiwanese population received health care services. NHI performs validation of medical charts to ensure the accuracy of documented diagnoses. The official longitudinal dataset derived from Taiwan NIH, Longitudinal Health Insurance Database 2000 (LHID 2000), contains all the original claim data of 1,000,000 beneficiaries enrolled in year 2000 randomly sampled from the year 2000 Registry for Beneficiaries of the NHI research database. The LHID 2000 has no statistically significant difference in gender distribution, nor age or healthcare cost between the enrollees in the LHID 2000 and the original NHI research database.

Selected cases and controls

From 1997 to 2001, a total of 371,185 subjects without previous diagnosis of urinary stone (ICD-9-CM codes 592 “calculus of the kidney and ureter”, 592.0 “calculus of the kidney”, 592.1 “calculus of the ureter” or 592.9 “urinary calculus, unspecified” and chronic periodontitis (ICD-9-CM codes 523.4 “chronic periodontitis”, 523.5 “periodontitis”, 523.8 “other specified periodontal diseases” or 523.9 “unspecified gingival and periodontal disease”) along with a minimal follow-up of eight years were enrolled. Of the study population, 16,292 subjects aged 30-70 years (8,237 males and 8,055 females) developed chronic periodontitis during the follow-up period and served as the study group. The definition of upper urinary tract stone (UUTS) was presence of the ICD-9-CM codes: 592.0, 592.1 or 592.9 at least twice, whereas the definition of chronic periodontitis was identified as ICD-9-CM code 523.4 with additional procedure code 91006C, 91007C, 91009B or 91010B.

Proven risk factors of urinary stone such as hypertension (ICD-9 codes 401-405) and diabetes mellitus (ICD-9 codes 250) were included into the multi-variable analysis. To increase our study validity, subjects with diagnosis of hypertension and diabetes mellitus for at least 3 times within one year were enrolled.

A comparison cohort without chronic periodontitis during the same period was randomly selected, frequency matched 1:3 (n=48876) for gender, age and comorbidities (diabetes, hypertension, hyperlipidemia). By the end of 2009, all subjects were followed up with a minimal of, eight years.

124 **Statistical Analyses**

125 The distribution of demographic status and comorbidities include age, sex, diabetes and
126 hypertension were compared between the CP and non-CP controls. Continuous variables were
127 evaluated by student's *t* test and categorical variables were analyzed by the Pearson chi-square
128 test. We compare the study population's characteristics by a crude model to match sex and age,
129 and the crude model was further then used again in the adjusted model to match the study
130 population with hypertension and diabetes.
131 Results are represented as hazard ratio (HR) with corresponding 95% confidence interval (95%
132 CI). Cox frailty proportional hazard regression model were used to determine the connection
133 between risk factors and the development of upper urinary tract stones. The UUTS-free survival
134 probability in patients with and without CP matched with and without hypertension and diabetes
135 during the follow up period was estimated using the Kaplan-Meier method. A log-rank test was
136 applied to generate figure data. We used SAS 9.2 statistics software (SAS Institute Inc., Cary, NC,
137 USA) to analyze data and statistical significance was considered if a conventional p value < 0.05.
138
139

Results

The demographic and clinical characteristics of the 65,168 subjects and controls, including 16,292 patients with CP and 48,876 control subjects were shown in table 1. Both groups had similar distribution of sex and age, and were predominantly male (50.6%) and 31-40 years (40.5 years) of age. Diabetes was more prevalent in the CP group at baseline (17.6% versus 15.9%, p<0.001). Overall, after at least eight-year follow-up, analysis demonstrate CP subjects have greater percentage for further development of UUTS than the controls (Hazard ratio 1.14, 95% confidence interval 1.08-1.20, *p*-values < 0.001), specifically, 1,761 (10.8%) of the study subjects, and 4,775 (9.8%) of controls developed UUTS (Table 2). Table 3 represent the association between UUTS and subjects' characteristics. Age, sex, diabetes and hypertension were both associated with developing UUTS. (all *p*-values < 0.001). After adjusting for age, gender, hypertension and diabetes, the Cox regression model fitted based on the study subjects and controls, showed that patients with CP still represent a significantly increased risk of developing UUTS. (HR = 1.14, 95%CI = 1.08–1.20, p<0.001)(Table 4). A Kalplan-Meier analysis showed that, during the 13-year study period, the overall cumulative incidence of UUTS was 19.2% higher for patients with CP than for those who did not have CP (p< 0.001, Figure 1).

Discussions

In this nationwide population-based retrospective cohort study, a greater percentage of subjects with CP develop UUTS than those without chronic periodontitis. CP increased the risk of developing subsequent UUTS. After adjusting for hypertension and diabetes, regression analysis still demonstrate CP as an independent factor for UUTS.

To date there is no study ever to explore the association between CP and UUTS. It appears that these two diseases share metabolic syndrome (MetS) as a common risk factor, which includes a spectrum of the following medical conditions: dysglycemia, dyslipidemia, visceral obsesity, and hypertension. In longitudinal and cross-sectional studies, there is positive correlation between MetS and CP—as the number of MetS components in an individual increases, so does the risk of periodontitis. (Kaye et al., 2016; Lee et al., 2015). The postulated mechanism for this association is well studied with dysglycemia, a key feature of MetS. Enhanced production of irreverible advanced glycation end product (AGE) in hyperglycemia state may result in defective constitution of extracellular matrix component, resulting in compromised tooth supporting tissue, devastated apparatus and eventual teeth exfoliation (Gurav et al., 2013). In addition, through the induction of IL-1b, TNF-a and PGE2 in dysglycemic state, increased oxidative stress may be associated with increased expression in receptor activator of nuclear factor kappaB ligand (RANKL), which plays a critical role in periodontal bone resorption (Wu et al., 2015). In a meta-analysis study studying MetS and urolithiasis, result showed patients with three or more MetS traits tended to have higher prevalence of urolithiasis (Wong et al., 2016), which is in similar to the relationship of MetS and periodontitis. Interestingly, patients who have two or more MetS factors tend to have higher prevalence of uric acid stones and lower prevalence of calcium phosphate stones, but the relative frequency of calcium oxalate stones remains regardless of the number of MetS factors (Kadlec et al., 2012). Higher frequency of uric acid stones in MetS patients can possibly be explained by a consequence of acidic urine, caused by impaired ammonia excretion and increase endogenous acid production secondary to insulin resistance (Strohmaier et al., 2012).

However, while CP and urolithiasis are both associcated with MetS, especially hyperglycemia and hypertension (Wong et al., 2016), after adjusting for diabetes and hypertension, CP remains an independent risk factor for developing UUTS. Due to the wide spectrum of endocrine and urine abnormality in urolithiasis patients, it may be more rational to investigate the abnormal finding

in chronic periodontitis patients and correlate with pathophysiology of urolithiasis. Given that periodontitis is characterized by tissue and bone destruction, serum calcium level, bone metabolism and specifically bone remodeling are altered during disease progression (Yoshihara et al., 2009; Schulze-Späte et al., 2015). In a recent study, Amarasena et al.,(2008) evaluated 266 Japanese subjects aged 70 years and assess relation of baseline serum calcium and the periodontal disease progression with six consecutive years follow up. The finding indicates subjects with low serum calcium level have a significantly higher chance of developing periodontal disease. This is corroborated in the Buffalo OsteoPerio study, which followed periodontal condition in 1,025 postmenopausal women for 5 years, and concluded that women with severe periodontitis and osteoporosis may exhibit accelerated bone loss over time (LaMonte et al., 2013). Higher rate of recurrent perdiodontits can also be expected in subjects with osteoporosis after periondontal treatment compared to the individuals with normal skeletal bone marrow density (BMD) (Gomes-Filho et al., 2013). Nonetheless, in another observational, prospective study evaluating men 65 years and older, although lower vitamin D and higher level of PTH were observed in severe periodontitis patients, these measures were not associated with progression. Additionally, bone metabolism markers were not associate with ~~periodontis~~ severity, but men with baseline lower levels of bone remodeling markers tend to have greater improvement in periodontitis (Schulze-Späte et al., 2015). On the other hand, the pathophysiological mechanisms for urolithiasis are complex and diverse, which include hypercalciuria, hyperuricosuria, hypocitraturia, hyperoxalateuria and abnormalities in urine pH (Pak, 1991). The mineral composition of stone is calcium oxalate or calcium phosphate in 80% of urolithiasis patients, whereas uric acid, struvite and cystine stone represent the rest. Formation of the crystal stone can happen from supersaturation of these crystalline material in urine, which is common when daily urine output is less than 2 liters (Ratkalkar & Kleinman, 2011) Hypercalciuria is the most common abnormal finding in the calcium urolithiasis patients, which can be found in 30-60% of them, and may result in supersaturation of urinary calcium salts (Pak et al., 1980). In hypercalciuric kidney stone formers, osteoporosis by mean of T-score < -2.5 is a prevalent finding. Moreover, hypercalciuria is ~~prevalentin~~ postmenopausal women, and also represent an important predictor for low bone mass (Giannini et al., 2003)

In our study, we only ~~enroll~~ patients between 30-70 years, which is the vast majority of the working population in Taiwan, therefore these findings cannot be extrapolated to subjects in

different age ranges. Male to female ratio is 1.69 in further UUTS occurance in our study, this ratio is higher in correspondence with previous Taiwanese population study, in which is ratio is 1.55 after age adjustment and greater than US population (Huang et al., 2013; Penniston et al., 2011).

Although this study detected association of chronic periodontits with subsequent UUTS development aided by the use of national database, our results need to be carefully intepretated by knowing its limitation. First, the data were obtained from NHI database, therefore certain patient information, including blood pressure and serum glucose, cannot be obtained, which makes the diagnosis less accurate than those made through standardized procedures. Second, other confounding factors such as personal health behavior, diet, lifestyle, height, weight, waistline measurements, drinking and cigarette smoking could not be adjusted in the NHIRD administrative data set. Lastly, we identified patients by diagnostic code (ICD-9), and increased the accuracy of the UUTS diagnosis by the presence of the ICD code twice and increased the accuracy of chronic periodontitis diagnosis by additional procedure code. However, we cannot evaluate the severity of disease and the composition of UUTS. Further prospective randomized study may be needed to elucidate the finding of this study and investigate the cause of UUTS in patients with chronic periodontitis.

Conclusion

By using population based database with a minimum eight year follow-up of chronic periodontitis in Taiwan, we discovered CP increase the risk of developing UUTS. CP patients receiving treatment for periodontitis should also be given the body of knowledge of its connection with further development of UUTS.

References

Amarasena N, Yoshihara A, Hirotomi T, Takano N, Miyazaki H. Association between serum calcium and periodontal disease progression in non-institutionalized elderly. Gerodontology. 2008;25(4):245-50. Epub 2008/03/31. doi: 10.1111/j.1741-2358.2007.00211.x. PubMed PMID: 18380783.

Armitage GC, Research SiaTCotAAoP. Diagnosis of periodontal diseases. J Periodontol. 2003;74(8):1237-47. doi: 10.1902/jop.2003.74.8.1237. PubMed PMID: 14514240.

Eke PI, Dye BA, Wei L, Thornton-Evans GO, Genco RJ, CDC Periodontal Disease Surveillance workgroup: James Beck (University of North Carolina CH, U. S. A.), Gordon Douglass (Past President, American Academy of Periodontology), R.y Page (University of Washin. Prevalence of periodontitis in adults in the United States: 2009 and 2010. J Dent Res. 2012;91(10):914-20. Epub 2012/08/30. doi: 10.1177/0022034512457373. PubMed PMID: 22935673.

Giannini S, Nobile M, Dalle Carbonare L, Lodetti MG, Sella S, Vittadello G, et al. Hypercalciuria is a common and important finding in postmenopausal women with osteoporosis. Eur J Endocrinol. 2003;149(3):209-13. PubMed PMID: 12943523.

Gomes-Filho IS, Oliveira TJ, Passos JS, Cerqueira EeM, da Cruz SS, Barreto ML, et al. Effect of osteoporosis on periodontal therapy among post-menopausal women. Gerodontology. 2013;30(1):40-8. Epub 2012/03/16. doi: 10.1111/j.1741-2358.2012.00643.x. PubMed PMID: 22420371.

Gurav AN. Advanced glycation end products: a link between periodontitis and diabetes mellitus? Curr Diabetes Rev. 2013;9(5):355-61. PubMed PMID: 23845077.

Hall PM. Nephrolithiasis: treatment, causes, and prevention. Cleve Clin J Med. 2009;76(10):583-91. doi: 10.3949/ccjm.76a.09043. PubMed PMID: 19797458.

Huang WY, Chen YF, Carter S, Chang HC, Lan CF, Huang KH. Epidemiology of upper urinary tract stone disease in a Taiwanese population: a nationwide, population based study. J Urol. 2013;189(6):2158-63. Epub 2013/01/09. doi: 10.1016/j.juro.2012.12.105. PubMed PMID: 23313204.

Jounai N, Kobiyama K, Takeshita F, Ishii KJ. Recognition of damage-associated molecular patterns related to nucleic acids during inflammation and vaccination. Front Cell Infect Microbiol. 2012;2:168. Epub 2013/01/08. doi: 10.3389/fcimb.2012.00168. PubMed PMID: 23316484; PubMed Central PMCID: PMCPMC3539075.

Kadlec AO, Greco K, Fridirici ZC, Hart ST, Vellos T, Turk TM. Metabolic syndrome and urinary stone composition: what factors matter most? Urology. 2012;80(4):805-10. Epub 2012/07/13. doi: 10.1016/j.urology.2012.05.011. PubMed PMID: 22795374.

Kaye EK, Chen N, Cabral HJ, Vokonas P, Garcia RI. Metabolic Syndrome and Periodontal Disease Progression in Men. J Dent Res. 2016;95(7):822-8. Epub 2016/03/29. doi: 10.1177/0022034516641053. PubMed PMID: 27025874; PubMed Central PMCID: PMCPMC4914866.

LaMonte MJ, Hovey KM, Genco RJ, Millen AE, Trevisan M, Wactawski-Wende J. Five-year changes in periodontal disease measures among postmenopausal females: the Buffalo OsteoPerio study. J Periodontol. 2013;84(5):572-84. Epub 2012/07/19. doi: 10.1902/jop.2012.120137. PubMed PMID: 22813344.

Lee KS, Lee SG, Kim EK, Jin HJ, Im SU, Lee HK, et al. Metabolic syndrome parameters in adolescents may be determinants for the future periodontal

diseases. J Clin Periodontol. 2015;42(2):105-12. Epub 2015/01/20. doi: 10.1111/jcpe.12338. PubMed PMID: 25469423.

Pak CY. Etiology and treatment of urolithiasis. Am J Kidney Dis. 1991;18(6):624-37. PubMed PMID: 1962646.

Pak CY, Britton F, Peterson R, Ward D, Northcutt C, Breslau NA, et al. Ambulatory evaluation of nephrolithiasis. Classification, clinical presentation and diagnostic criteria. Am J Med. 1980;69(1):19-30. PubMed PMID: 6247914.

Pearle MS, Calhoun EA, Curhan GC, Project UDoA. Urologic diseases in America project: urolithiasis. J Urol. 2005;173(3):848-57. doi: 10.1097/01.ju.0000152082.14384.d7. PubMed PMID: 15711292.

Penniston KL, McLaren ID, Greenlee RT, Nakada SY. Urolithiasis in a rural Wisconsin population from 1992 to 2008: narrowing of the male-to-female ratio. J Urol. 2011;185(5):1731-6. Epub 2011/03/21. doi: 10.1016/j.juro.2010.12.034. PubMed PMID: 21420112; PubMed Central PMCID: PMCPMC3280819.

Ratkalkar VN, Kleinman JG. Mechanisms of Stone Formation. Clin Rev Bone Miner Metab. 2011;9(3-4):187-97. doi: 10.1007/s12018-011-9104-8. PubMed PMID: 22229020; PubMed Central PMCID: PMCPMC3252394.

Saigal CS, Joyce G, Timilsina AR, Project UDiA. Direct and indirect costs of nephrolithiasis in an employed population: opportunity for disease management? Kidney Int. 2005;68(4):1808-14. doi: 10.1111/j.1523-1755.2005.00599.x. PubMed PMID: 16164658.

Scales CD, Smith AC, Hanley JM, Saigal CS, Project UDiA. Prevalence of kidney stones in the United States. Eur Urol. 2012;62(1):160-5. Epub 2012/03/31. doi: 10.1016/j.eururo.2012.03.052. PubMed PMID: 22498635; PubMed Central PMCID: PMCPMC3362665.

Schenkein HA. Host responses in maintaining periodontal health and determining periodontal disease. Periodontol 2000. 2006;40:77-93. doi: 10.1111/j.1600-0757.2005.00144.x. PubMed PMID: 16398686.

Schulze-Späte U, Turner R, Wang Y, Chao R, Schulze PC, Phipps K, et al. Relationship of Bone Metabolism Biomarkers and Periodontal Disease: The Osteoporotic Fractures in Men (MrOS) Study. J Clin Endocrinol Metab. 2015;100(6):2425-33. Epub 2015/04/09. doi: 10.1210/jc.2014-4180. PubMed PMID: 25856210; PubMed Central PMCID: PMCPMC4454801.

Shields AM, Panayi GS, Corrigall VM. Resolution-associated molecular patterns (RAMP): RAMParts defending immunological homeostasis? Clin Exp Immunol. 2011;165(3):292-300. Epub 2011/06/14. doi: 10.1111/j.1365-2249.2011.04433.x. PubMed PMID: 21671907; PubMed Central PMCID: PMCPMC3170978.

Stamatelou KK, Francis ME, Jones CA, Nyberg LM, Curhan GC. Time trends in reported prevalence of kidney stones in the United States: 1976-1994. Kidney Int. 2003;63(5):1817-23. doi: 10.1046/j.1523-1755.2003.00917.x. PubMed PMID: 12675858.

Strohmaier WL, Wrobel BM, Schubert G. Overweight, insulin resistance and blood pressure (parameters of the metabolic syndrome) in uric acid urolithiasis. Urol Res. 2012;40(2):171-5. Epub 2011/08/25. doi: 10.1007/s00240-011-0403-9. PubMed PMID: 21866382.

Wong Y, Cook P, Roderick P, Somani BK. Metabolic Syndrome and Kidney Stone Disease: A Systematic Review of Literature. J Endourol. 2016;30(3):246-53. Epub 2016/01/22. doi: 10.1089/end.2015.0567. PubMed PMID: 26576717.

Wu YY, Xiao E, Graves DT. Diabetes mellitus related bone metabolism and periodontal disease. Int J Oral Sci. 2015;7(2):63-72. Epub 2015/06/26.

356 doi: 10.1038/ijos.2015.2. PubMed PMID: 25857702; PubMed Central
357 PMCID: PMCPMC4817554.

358 Yoshihara A, Deguchi T, Hanada N, Miyazaki H. Relation of bone turnover
359 markers to periodontal disease and jaw bone morphology in elderly
360 Japanese subjects. Oral Dis. 2009;15(2):176-81. doi: 10.1111/j.1601-
361 0825.2008.01511.x. PubMed PMID: 19207487.
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Table 1(on next page)

Demographic characteristics of patients with chronic periodontitis and controls

Table 1. Demographic characteristics of patients with chronic periodontitis and controls

	Patients with CP (n=16292)-		Controls (n=48876)		
Variable	Total No.	%	Total No.	%	*P* value
Sex					1.00
Male	8237	50.6%	24711	50.6%	
Female	8055	49.4%	24165	49.4%	
Age					0.634
<31	526	3.2%	1840	3.8%	
31-40	6592	40.5%	19654	40.2%	
41-50	5641	34.6%	16451	33.7%	
51-60	2360	14.5%	7239	14.8%	
61-70	1173	7.2%	3692	7.6%	
Personal history					
Diabetes	2870	17.6%	7782	15.9%	<0.001
Hypertension	4870	29.9%	14983	30.7%	0.067

Table 2(on next page)

Crude HR for new-onset upper urinary tract stone (UUTS) among patients with chronic periodontitis and comparison controls

Table 2. Crude HR for new-onset upper urinary tract stone (UUTS) among patients with chronic periodontitis and comparison controls

New-onset UUTS	Total Sample (n=65168)		Patients with CP (n=16292)		Comparison controls (n=48876)	
8-year follow up	No.	%	No.	%	No.	%
Yes	6536	10.0	1761	10.8	4775	9.8
No	58632	90.0	14531	89.2	44101	90.2
Crude HR (95% CI)	-		1.14		1.00	

Table 3(on next page)

Demographic characteristics of subjects with and without new-onset upper urinary tract urolithiasis (UUTU) during follow-up

Table 3. Demographic characteristics of subjects with and without new-onset upper urinary tract stone (UUTS) during follow-up

	Subjects with UUTS (n=6536)		Subjects without UUTS (n=58632)		
Variable	Total No.	%	Total No.	%	*P* value
Age	Mean 44.8 ± 9.9		Mean 43.5± 9.7		< 0.001
Sex					< 0.001
Male	4107	62.8	28841	49.2	
Female	2429	37.2	29791	50.8	
Periodontitis					< 0.001
Yes	1761	26.9	14531	24.8	
No	4775	73.1	44101	75.2	
Diabetes					< 0.001
Yes	1379	21.1	9273	15.8	
No	5157	78.9	49359	84.2	
Hypertension					< 0.001
Yes	2591	39.6	17262	29.4	
No	3945	60.4	41370	70.6	

Table 4(on next page)

The risk for upper urinary tract stone among chronic periodontitis, hypertension and diabetes patients in Cox proportional hazard regression

Table 4. The risk for upper urinary tract stone among chronic periodontitis, hypertension and diabetes patients in Cox proportional hazard regression

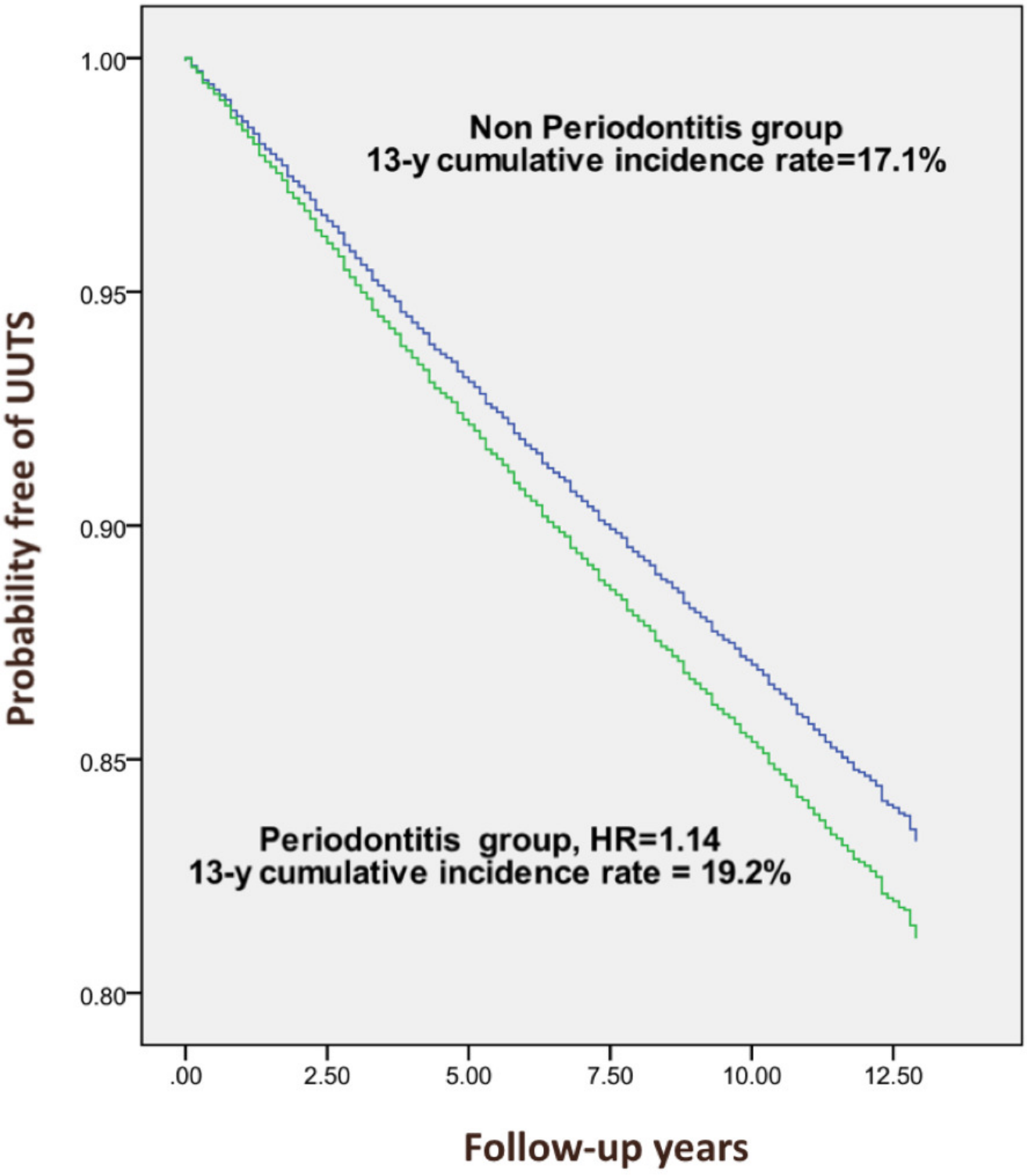
	Crude HR	95% CI	*P* value	Adjusted HR	95% CI	*P* value
Main Effect						
Chronic Periodontitis	1.14	1.08-1.20	<0.001	1.14	1.08-1.20	<0.001
Comorbidities						
Hypertension	1.35	1.28-1.44	<0.001	1.17	1.10-1.25	<0.001
Diabetes	1.48	1.41-1.55	<0.001	1.42	1.34-1.49	<0.001

Crude HR: relative hazard ratio

Ajusted HR: multivariable analysis including age, sex and cormorbidities

Figure 1

Probability free of upper urinary tract stone (UUTS) for periodontitis and non-periodontitis patients


Non Periodontitis group
13-y cumulative incidence rate=17.1%
Periodontitis group, HR=1.14
13-y cumulative incidence rate = 19.2%
Probability free of UUTS
1.00
0.95
0.90
0.85
0.80
.00
2.50
5.00
7.50
10.00
12.50
Follow-up years